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# CLINICAL NOTE

## WHY DO THE LUNGS CLEAR ULTRASONIC CONTRAST?*

RICHARD S. MELTZER, E. GLEN TICKNER and RICHARD L. POPP

Cardiology Division, Stanford University School of Medicine, Stanford, CA 94305, U.S.A. and Rasor Associates, Inc., Sunnyvale, California, U.S.A.

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**Abstract**—Peripherally injected ultrasonic contrast is removed by the lungs. The source of this contrast effect is microbubbles in the injected fluid. We studied bubble dynamics to attempt to explain their removal by the lungs. Commercially prepared precision microbubbles of 5–10 $\mu$m could be imaged using standard *M*-mode echocardiographic equipment. Thus, absence of contrast in left atrial echocardiogram after peripheral contrast injections implies that bubbles of this size are absent, though they are small enough to traverse the pulmonary capillary "sieve". Calculations show that a bubble of diameter small enough to get through these capillaries (mean size 8 $\mu$m) will totally dissolve due to surface tension effects, in a time shorter than the pulmonary capillary to left atrial circulation time.

*Key words*: Echocardiography, Ultrasonic contrast, Microbubbles.

Echocardiographic contrast was first reported during indocyanine green injection in the catheterization laboratory (Gramiak, 1969). Although many empiric observations have been made since then (Feigenbaum *et al.*, 1970; Hagemeijer, 1977), theoretic understanding of ultrasound contrast has moved slowly. The following is an attempt to explain a well-known echocardiologic observation—the disappearance of ultrasound contrast from blood during passage through the lungs. Prior investigations suggest that the source of ultrasonic contrast in peripherally injected solutions is microbubbles (Kremkau *et al.*, 1970; Barrera *et al.*, 1978). Data from our laboratory confirm this, and suggest that the microbubbles in shaken saline and indocyanine green are of a wide spectrum of sizes (Meltzer *et al.*, 1979). If such bubbles are much larger than the pulmonary capillary diameter of about 8 $\mu$m (Weibel, 1963; Weibel, 1962), they will be held up by the pulmonary capillary "sieve". This is the explanation usually given for their disappearance. Those that are originally smaller that 10 $\mu$m, that are fractured into fragments of this size, or that have their gas partly resorbed and "shrink" until they are smaller than 10 $\mu$m in diameter should be able t traverse the capillaries and emerge int the pulmonary veins. We wished to learn why such small bubbles were not detectable in the left heart by ultrasound. We thought that either these small bubbles were present but not detectable by standard echocardiographic techniques, or that they somehow disappeared from the circulation by a mechanism separate from the capillary sieve action that should remove bubbles larger than 10 $\mu$m.

### METHODS

To ascertain whether microbubbles with a nominal diameter of 10 $\mu$m can be imaged by commercially available echocardiographic equipment, the following test was performed. Pure nitrogen microbubbles were created in a supersaturated solution of 42 DE corn syrup diluted with distilled water 4 : 1. This liquid had a measured viscosity of 1000 cp at 20°C. A surfactant, Tween 80, was added to this solution in the amount of 2% by volume. This surfactant served two useful purposes: first, it decreased coalescence of the newly created microbubbles; and second, it reduced the pressure within the bubble caused by surface tension and thereby decreased its dissolving rate. The degree of supersaturation of the syrup was adequate to stabilize microbubbles long enough to transport them via a large syringe. Hence, the microbubbl s were delivered t the experimental set-up at the same diameters as created. These microbubbles were measured with a micr sc pe and found t be $10 \pm 5$ $\mu$m in diameter.

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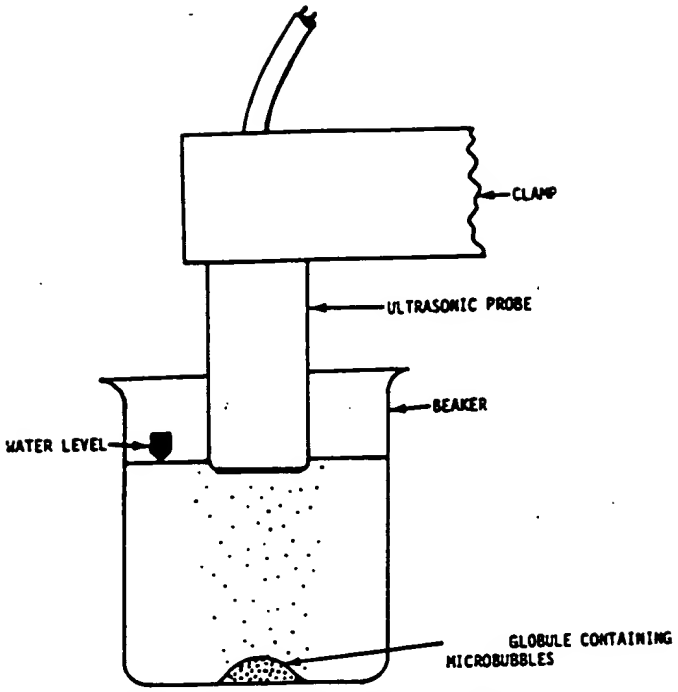


Fig. 1. Schematic showing experimental set-up for bubble rise test.

The experimental set-up, shown schematically in Fig. 1, consisted of a large beaker filled with water degassed by prolonged standing exposure to air. A 2.25 MHz acoustically focused transducer was placed just under the surface of the water aiming downward. A SKI Ekoline 20A *M*-mode ultrasonograph was used to record echoes.

Lack of signals recorded from the beaker prior to the injection of any material assured us the beaker was free of invisible microbubbles or other echo-producing materials. Then a mass (1 ml) of the syrup containing approx. 100,000 microbubbles was injected, with the syringe and a long needle, onto the bottom of the beaker. The dense syrup lay on the bottom and slowly began to dissolve. Also, the entrapped microbubbles rose slowly in the viscous syrup. The larger bubbles reached the drop interface first and rose in water. The purpose for using the viscous liquid was to permit this slow release of nitrogen bubbles and to grade somewhat the size. Visual identification of microbubbles rising from the viscous mass at the bottom of the beaker was performed using a bright side-light in a darkened room. The bubbles did not begin t dissolve until they left the supersaturated mass and reached the unsaturated water, and then dissolved as they rose in the water.

## RESULTS

Single microbubble (or family of microububble) trajectories could be recognized on the *M*-mode echocardiographic recording (Fig. 2). Because of the nature of the bubble release from the viscous globule, fairly uniform sized bubbles are released at any given time. Hence, one measures the slope of an entire family to obtain their size by computation based upon Stokes' law for frictional resistance (Happle and Brenner, 1965). The rate of rise of the slowest of these was 0.023 mm/sec corresponding to a bubble size of 6.5 $\mu$m; the fastest was 3.6 mm/sec, representing a few bubbles of 80 $\mu$m probably formed by coalescence of the smaller bubbles or air introduced during the procedure of placing the syrup-containing microbubbles at the bottom of the beaker. The ultrasonic trajectories correspond with the visual size of bubbles in the beaker seen using the bright side-light. Prolonged recording of some small bubbles (Fig. 2) apparently was due to a capsule of syrup slowing the dissolution of the bubbles, nevertheless the bubble size can be calculated from the slope measured for a single echo tracing.

## BUBBLE DISSOLUTION CALCULATIONS

Studies of bubble dissolution dynamics have appeared in the literature over the years


Fig. 2. *M*-mode echocardiographic strip chart recording of microbubbles rising in a beaker of degassed water. The slope of the bubbles shown by the arrow is 0.023 mm/sec, corresponding to a calculated size of 6.5 $\mu$m. Note the more rapid rate of rise of larger bubbles or groups of bubbles earlier (to the left in this panel) near the label "1 sec".

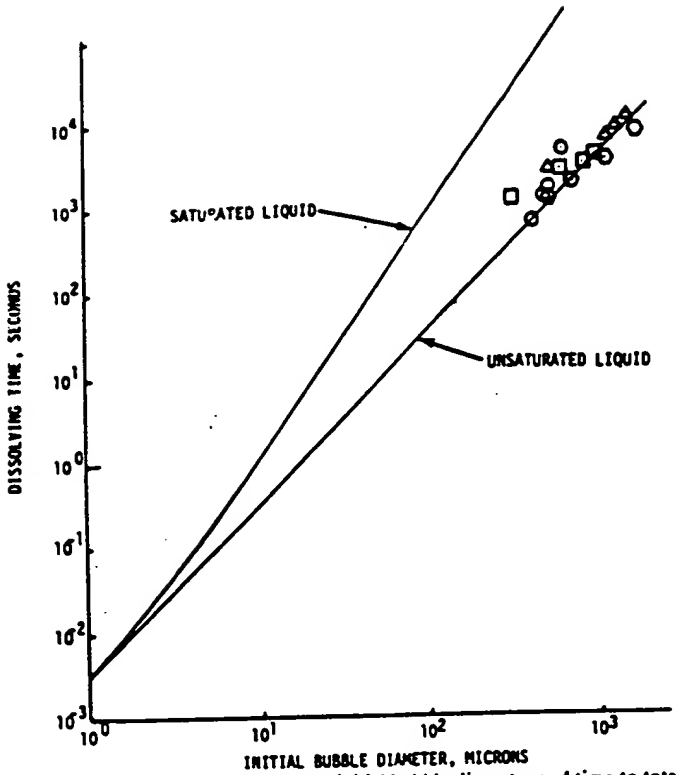


Fig. 3. Log-log plot showing relationship between initial bubble diameter and time to total dissolution. Calculated based on theory presented by Epstein and Plesset (1950), assuming a bubble of nitrogen in degassed whole blood but not correcting for flow effects. Data by Yang *et al.* (1971) for unsaturated liquids given by symbols (⊙, oxygen bubbles in human blood; ⊡, oxygen bubbles in canine blood; △, nitrogen bubbles in human blood plasma; and ⊙ oxygen bubbles in human blood plasma).

(Epstein, 1950; Ward, 1975). Epstein and Plesset (1950) examined gas bubbles dissolving in liquid solutions, and others have extended this work to account for chemical reactions, bubble/liquid motion and bubble gas composition. Bubbles will shrink and disappear by diffusion in unsaturated solutions, and bubbles will also shrink in saturated solutions because of surface tension effects. The very small bubbles necessary to traverse the capillaries would have a high internal pressure due to the high surface tension effect that goes along with the small size. Gas inside the bubble would rapidly diffuse down its concentration gradient into the surrounding fluid, decreasing the bubble size and increasing the surface tension. This would accelerate the process, causing rapid total dissolution for this population of very small microbubbles. The time for total dissolution, taking into account the effects of surface tension, is presented in Fig. 3 for both saturated and unsaturated solutions. An 8 $\mu$m bubble will completely diss lve in between 190 and 550 msec depending upon the degree of saturation of the surrounding fluids. Data from Yang *et al.* (1971) indicates that nitrogen bubbles in blood plasma dissolve as if in an unsaturated solution. Thus the expected time of complete dissolution will be close to 190 msec. All other effects, such as wiping away the diffusion boundary layer, can decrease this time dramatically (Yang *et al.*, 1971). Hence, this figure should be considered conservative.

In man, blood transit time from the pulmonary capillaries to the left atrium is two seconds or more (Hamilton, 1963). Hence, if bubbles smaller than 8 $\mu$m dissolve completely in less than 190 msec, they cannot appear in the left atrium.

## DISCUSSION

We were not surprised to find that microbubbles small enough to pass through the pulmonary capillary sieve can be imaged with currently available echocardiographic equipment, since we know that we c uld image 38 and 140 $\mu$m micr bubbles from pri r experience (Carroll *et al.*, 1980). We observed a spectrum f rates of rise and bubbl size, the same phenomenon as seen when bubbles

rise in carbonated water after a bottle has been opened. As seen in Fig. 2, some sl pes of rise correspond t bubble sizes below the pulmonary capillary diameter, and thus if these bubbles were present on the left side of the heart they should be imaged during routine echocardiographic examinations. A possible exception to this thesis is that our *in vitro* model does not correspond to *in vivo* conditions, and perhaps echoes of low intensity might be so scattered and attenuated by body tissues that they could not be seen. We consider this unlikely, however, since slightly larger microbubbles (75 $\mu$m) gave a qualitatively similar contrast effect both *in vivo* and *in vitro* in our laboratory (Meltzer *et al.*, 1980).

The large difference in acoustic impedence between the liquid blood and gas-containing bubble produces relatively high intensity echoes. The desire to resolve neighboring bubbles as separate echoes or resolve both surfaces of a single bubble could be a problem with low resolution systems, but we are only concerned here with the presence or absence of echoes. The echo amplitudes from these microbubbles are well within the range detectable by our equipment.

Relatively large bubbles may be fractured in the right heart and will continuously shrink because of diffusion as mentioned above. The disappearance time calculated here explains why microbubbles larger than about 5 $\mu$m are not present in the left atrial and left ventricular blood after peripheral venous injections, in the absence of right-to-left shunts or abnormal pulmonary arteriovenous connections that could provide rapid transport to the left heart (Lewis *et al.*, 1978). We conclude that the reason ultrasonic contrast is removed by capillary networks is that microbubbles larger than the capillary size are held up by the "sieve" action of the network, and those that become small enough to get through the capillaries dissolve very rapidly. The detection in the left heart of microbubbles, in injected indocyanine green dye, due to unusually rapid flow through a pulmonary fistula is interesting (Lewis *et al.*, 1978). This dye lowers surface tension and "stabilizes" or changes the diss lution characteristics of microbubbles (Meltzer *et al.*, 1980). The size of the micr bubbles traversing a pulmonary fistula t enter the left heart has not been measured. Perhaps use of surfactants, or inhalation of specially constituted gas mixture after peripheral micr bubble injection, c uld enable microbubbles t survive long en ugh after transport thr ugh the lungs to be consistently imaged on the left side of the heart.

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